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THE ASSAY, CHARACTERISTICS, COMPOSITION, AND ORIGIN OF OPIUM

No. 11

Assay of Raw Opium for Morphine

A study of the Method of Professor Erich Knaffl-Lenz

Laboratories of the S.E.M.P.A. Company, Paris.

In continuation of the international programme of scientific research undertaken pursuant to resolutions 159 II C (VII) and 246 F (IX), adopted by the Economic and Social Council on 3 August 1948 and 6 July 1949 respectively, the Secretary-General is presenting the following paper prepared by chemists of the S.E.M.P.A. Company, in which the method of assay given in ST/SOA/SER.K/3 is further considered and modified.

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ASSAY OF RAW OPIUM FOR MORPHINE

A Study of the Method of Professor Erich Knaffl-Lenz

(ST/SOA/SER.K/3, 1 August 1951).

Work done in the laboratories of the Company S.E.M.P.A., Paris.

1. The Knaffl-Lenz method has been tried experimentally on a Turkish opium. It gave the results described by the author: constant and higher by 0.3 in the percentage of morphine than the Harrison assay.

2. Because the first filtration of the opium extracts appeared to be difficult through a crucible-filter, the following method was adopted: filtration through a Buchner funnel, diameter 5-6 cm., with two layers of filter paper; for returning the opium into the flask, use of a spatula and a brush without lifting off the paper; filtration of the aqueous solution saturated with sodium sulphate through a layer of 10 g of fine washed sand.

3. Another inconvenience is the formation of emulsion and the precipitation of sodium sulphate during the extraction of morphine. It is well to prepare the solution of sodium sulphate at least two days ahead of time and to keep it at a temperature of 15° to 20° C. In spite of these precautions, sometimes an annoying emulsion still forms.

4. It was found necessary to agitate the alkali solution twice with benzene to eliminate the secondary alkaloids completely.

5. The analysis requires much longer than the 2-3 hours stated. To this must be added sufficient time to dry the opium, pulverize it and dry it again. The exact determination of the loss of weight is important. In fact, we needed a day and a half to apply this method.

6. The morphine obtained by evaporation of the solvent is still very coloured. The fact that the result is generally higher than the Harrison assay does not prove that it is exact.

7. It seemed good in the light of previous experiences to try to modify this method while keeping its best points, in order to obtain a more pure morphine prior to titration.

Principle of the Modified Method

8. We came back to extraction with lime water, done at room temperature, which already provides for the separation of resins, organic acids, colouring substances, and also part of the secondary alkaloids. It is possible to perform this extraction totally, without dividing it up, by using a method suggested by M. MASCRE for the assay of opium. (Ann. Pharm. Fr. 3, n° 3-4 - 1945, p. 111).

9. Though this extraction requires a little more time it is easily applied and in fact less tedious, because the filtrations and the extractions using solvents are easier to perform. The prior drying of opium can be avoided which saves time and eliminates a possible source of error.

10. The excess of lime is afterwards eliminated by precipitation as carbonate in the presence of an excess of sodium hydroxide; the remaining codeine is extracted with benzene.

11. After concentration of this solution brought to pH_4, the greater part of the tarry material is precipitated by sodium sulphate and the morphine extracted, after addition of sodium carbonate, by the solvents recommended by Kraffl-Lenz. (It has been verified that in presence of ammonia, the extraction is incomplete.)

12. After evaporation, one can purify the morphine and crystallize it before the titration.

13. The purity of the morphine obtained would be better if one could find a more selective solvent, and esp :ially one not miscible with water.

14. Thus modified, this method can be applied within a day and a half. It gave constant results close to those of Harrison and of the International method.

15. It constitutes a new milestone towards the establishment of a basic method for the assay of morphine in raw opium, which will help in the future to find faster physical-chemical methods. This method can be applied without modification to the assay of morphine in poppy plant material or more exactly in the dry extract obtained from aqueous-alcoholic extracts of dried poppy plant material.

Description of the Modified Method

16. For the assay, crush 3 grammes of opium in a small mortar with 10 cc of water heated to 60°. When the opium is disintegrated as completely as possible,

add 1 g of calcium hydroxide and work to a very fine paste, then add 10 cc of cold water and stir for about 10 minutes. Filter through a crucible filter of fritted glass (No. 3 G 3) into a suction flask of 250 cc, so that the foam is not troublesome. Crush in the mortar 0.5 g of calcium hydroxide with 5 cc of water and transfer it to the crucible. Bring the caked residue into suspension again by means of a stirring rod; this operation must be done very carefully. To the fine paste obtained add 10 cc of water which has been used for rinsing the mortar, and again stir for several minutes before filtering by means of suction.

17. Wash the dry residue 3 times in the same way with 10 cc of cold water. Add 5 cc of water for mixing and another 5 cc of water before stirring and sucking dry. (These filtrations take 3/4 of an hour, but need little attention.)

18. Add hydrochloric acid to the alkaline solution to slight acidity (about 0.9 cc of acid, sp. gravity 1.19). Heat the solution to about 60° and add 5 cc of 5 N sodium hydroxide and 3 cc of a 10 per cent anhydrous sodium carbonate. Stir it and cool rapidly while letting the precipitate settle.

19. Filter through a crucible filter, first decanting the clear solution, and then carrying along the precipitate; and wash with the minimum amount of water.

20. The solution is diluted to 105 cc in a graduated flask. Transfer it without rinsing into a dry separatory funnel and agitate with 80 cc of hot benzene. Filter most of the water layer, cool it and measure from it exactly 70 cc corresponding to 2 grammes of opium.

21. Pour this solution into a small pyrex evaporating dish and add hydrochloric acid drop by drop to pH_4. Then concentrate on the steam bath ot 15 - 20 cc and again adjust to pH_4 if necessary. Then add 2 grammes of anhydrous sodium sulfate, which is rapidly dissolved by stirring with a glass rod. After cooling, filter through a very small pledget of cotton. The rinsing is done with a saturated solution of sodium sulphate (which has been left for 2 days at 15° - 20°) to which is added 0.5 cc 0.1 N HCl for each 100 cc. The dish and the funnel are washed with 2 cc of this solution. Then transfer the piece of cotton to the dish, and wash the funnel with 5 cc of wash solution. Then heat it for several minutes on a steam bath, cool, and filter it through a second pledget of cotton. Repeat this washing once more.

22. To the solution add 5 cc of a 10 per cent solution of anhydrous sodium carbonate. and extract by shaking with 80 cc of a mixture of chloroform and ethanol in the proportion of 3 to 2 (sp. gravity = 1.220). Then use successively 50, 20, and 20 cc of a mixture of chloroform - ethanol in the proportion of 3 to 1. (Specific gravity = 1.300). Shaking can be carried out without taking precautions; if a little emulsion is formed it can be broken easily by placing the separatory in a horizontal position for some seconds or by heating its bulb slightly, with the stopcock open, on a steam bath. It is necessary to wait before separating until the lower layer of solvents has become clear.

23. The entire mixed solvent solution is dried by shaking twice with anhydrous magnesium sulphate. Filter through cotton and wash the salt quickly with the solvent mixture. Finally evaporate the solution on a steam bath in an Erlenmeyer flask, and complete the evaporation by means of a vacuum pump.

24. The dried residue may be titrated directly - or purified by crystallization. (The more impure the morphine is with gummy substances, the greater is the risk of losing morphine in this purification and then the result will be too low.) Dissolve the residue in 2 cc of a mixture of methanol-benzene in a proportion of 1 to 3, then add 10 cc of water saturated with morphine, chilled with iced water for half an hour and filter off the morphine on a crucible-filter, washing with a few cc of cold benzene, then with ether. Dissolve the morphine remaining in the Erlenmeyer flask in 2 portions of 10 cc each of N/10 sulphuric acid and transfer the solution to the crucible in order to dissolve all the morphine; it is necessary to crush this morphine with a glass rod in the bottom of the crucible. Then wash through with water and titrate the excess of acid with N/10 sodium hydroxide in the presence of methyl red until the solution turns yellow.

25. One cc of N/10 acid corresponds to 0.0285 g of anhydrous morphine. The result obtained corresponds to 2 g of opium.